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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,188	05/11/2001	Paul R. Findell	3930-0911	7236

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EXAMINER
DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
1647	10

DATE MAILED: 05/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,188	FINDELL ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *3 and 15-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-36* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

Status of Application, Amendments and/or Claims

The information disclosure statements filed 18 October 2001 (Paper No. 5) and 30 July 2002 (Paper No. 6) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The amendment filed 25 February 2003 (Paper No. 9) has been entered in full.

Applicant's election of Group III (claims 1, 2, 4-9, 11-14, 36) and species election of mucosal epithelial cells and oral cancer with traverse of Group in Paper No. 9 is acknowledged. The traversal is on the grounds that it would be no serious burden to the Examiner to search and examine claims 1-14 and 36, the claims of Groups I-III. Applicant states that Groups I-III recite methods of treating disorders by administering an agent that effects processing of laminin 5 by a BMP-1 related protein. Applicant maintains that BMP-1, mTId, mTII-1 and mTII-2, share significant structural and functional homology and BMP-1 and mTId are splice variants encoded by the same gene. The BMP-1 related enzymes have similar activities with respect to processing of laminin 5 α3 and γ2 subunits.

Applicant's arguments have been fully considered and are deemed partly persuasive. The Examiner will rejoin Groups II and III. In addition, Groups VI (claim 25) will be rejoined with Group X (claim 30). Group I will not be rejoined with Groups II and III because Group I and Groups II-III encompass diverse patient populations. The Groups require search and consideration of different cancers, which may not overlap.

These forms of cancer exhibit different pathologies. A search on glioma would extend to include neoplasms of the brain and spinal cord. A search on neoplastic epithelial cells alone is very intricate. The searches would not be co-extensive.

The requirement is still deemed proper and is therefore made FINAL. Claims 1, 2, 4-14 and 36 are under examination. Claims 3, 15-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claim Objections

Claims 5 and 7 are objected to because of the following informalities: The instant claims are not limited to the elected (species) invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to a method of treating a

condition characterized by increased expression or activity of laminin 5, the method comprising administering to a subject in need an effective amount of an agent that affects processing of laminin 5 by a BMP-1 related protein, a method of treating cancer, the method comprising administering to a subject in need of an effective amount of an agent that affects processing of laminin 5 by a BMP-1 related protein, a method of treating a condition characterized by neoplastic epithelial cells, the method comprising administering to a subject in need an effective amount of an agent that affects processing of laminin 5 by a BMP-1 related protein and a method of treating squamous cell carcinoma, the method comprising administering to a subject in need an effective amount of an agent that affects processing of laminin 5 by a BMP-1 related protein. The specification teaches that compounds 1-3 inhibited the activity of BMP-1 related proteins (mT1d, mT11-1 and mT11-2) on the processing of laminin 5 ***in vitro*** (specification, Examples 2-8). The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure.

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between inhibition of laminin 5 processing by a BMP-1 related protein in the presence of an agent ***in vitro*** and method of treating a condition characterized by increased expression or activity of laminin 5, a method of treating cancer, a method of treating a condition characterized by neoplastic epithelial cells and a method of treating squamous cell carcinoma, the method comprising administering to a subject in need an effective amount of an agent that affects processing of laminin 5 by a BMP-1 related protein ***in vivo.*** The *in vitro*

experimental data presented is clearly not drawn to subjects with conditions characterized by increased expression or activity of laminin 5 or neoplastic epithelial cells, cancer or squamous cell carcinoma.

Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, pg. 4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In vitro*).

Dermer (Bio/Technology, March 1994, Vol.12, No. 3 pg. 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture

exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, increased frequency of endoapoptosis would be in any way correlated with increased risk of tumor progression.

Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Further, an anti-cancer agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition the target cell must not have an alternate means of survival despite action at the proper site for the drug. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the agent is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure that the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The peptide may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half-life of the protein and the *in vitro* tests of record do not sufficiently duplicate the conditions that occur *in vivo*. In addition, the peptide may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the peptide has no effect, circulation into the target area may be

insufficient to carry the peptide and a large enough local concentration may not be established.

Furthermore, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraph).

The specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Due to the large quantity of experimentation necessary to treating a condition characterized by increases expression or activity of laminin 5 or neoplastic epithelial cells, cancer, or squamous cell carcinoma in a subject, the lack of direction/guidance presented in the specification regarding same, the absence of working examples

directed to same, the complex nature of the invention, the contradictory state of the prior art, and the unpredictability of the anticancer treatments (see discussion above and recited references), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 36 is rejected under 35 U.S.C. 102(b) as being anticipated by Amano *et al.* (Journal of Investigative Dermatology, Vol. 108, No. 4, pg, 542, Meeting Info: Annual Meeting of the Society for Investigative Dermatology. Washington, DC, USA April 23-23, 1997). The instant claim is drawn to a method of affecting laminin 5 expression or activity, the method comprising contacting laminin 5 with an effective amount of an agent that affects processing of laminin 5 by a BMP-1 related protein.

Amano *et al.* teach that recombinant BMP-1 cleaves γ2 chain of laminin 5 *in vitro*. Amano *et al.* teach that inhibition of γ2 cleavage by EDTA or o-phenanthroline is consistent with the inhibition of BMP-1.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
May 12, 2003

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER